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EDITORIAL

Beyond a glomerulocentric view of inflammation

It has long been recognized that the kidney's tubulointerstitial space is affected during the course of glomerular disease, and that the severity of this accompanying interstitial injury (inflammation, apoptosis, tubular atrophy, and fibrosis) influences the impact of a glomerulopathy on renal function. Release of pro-inflammatory factors from inflamed glomeruli into the interstitium has been proposed as a pathogenic link between the glomerular and interstitial compartments. Recent work, including the investigation presented by Isbel et al in this issue of *Kidney International*, suggest an alternative mechanism—a more direct and perhaps independent role of the tubular epithelium in mediating the interstitial inflammation [1]. Tubular cells can be induced to express a number of immune modulators, some of which are listed in Table 1. These tubule-derived factors must be considered when designing therapies to control renal inflammation.

Isbel et al provide evidence that renal tubular epithelium is a major site of production of macrophage colony-stimulating factor (M-CSF) during experimental renal injury [1]. Renal M-CSF expression was studied in rodent models of anti-glomerular basement membrane (GBM) glomerulonephritis (GN), and unilateral ureteral obstruction, a tubulointerstitial process without glomerular involvement. The key finding of this study was the marked induction of M-CSF mRNA and protein expression in the cortical tubules of the injured kidneys. Importantly, M-CSF was also found in nephritic glomeruli, but *not* glomeruli from obstructed kidneys. There was a correlation between tubular M-CSF, interstitial macrophage accumulation and proliferation, decline in creatinine clearance, and proteinuria. M-CSF was also detected in urine after renal injury. Consistent with tubular M-CSF production, human tubular epithelial cells have been shown to release M-CSF in vitro [2], and, in a mouse model of ischemia-reperfusion injury, where the prominent lesion is tubular, not glomerular, M-CSF mRNA (whole kidney) was rapidly up-regulated [3]. It should be pointed out, however, that most studies to date have found tubular M-CSF to be much lower, or negligible, compared to glomerular M-CSF, at least in the context of GN [4–6]. Isbel et al suggest that this discrepancy may be due to differences in the antibodies used to detect M-CSF. However, the lack of significant tubular in situ hybridization for M-CSF mRNA in some of these studies indicates that antibody differences do not fully account for the discrepancy.

M-CSF is a hematopoeitic growth factor that is important in the differentiation, survival, and proliferation of mature monocytes and macrophages [reviewed in 7]. M-CSF is also a regulatory cytokine that activates macrophage cytokine production, enhances macrophage responsiveness to secondary signals, and promotes chemotaxis [7]. Because glomerular M-CSF expression has been observed in both experimental and human GN [4–6], and correlates with renal macrophage accumulation, activation, and proliferation, as well as glomerular injury and proteinuria [5, 6, 8, 9], a pro-inflammatory role for this growth factor/cytokine has been assumed. Consistent with such a role, the exogenous transfer of the *M-CSF* gene into kidneys of autoimmune MRL-*Fas*^{lpr} mice, but not normal mice, causes local tissue injury accompanied by extensive macrophage infiltration [10]. However, while M-CSF is present in diseased kidneys, and can induce renal inflammation in appropriate settings, there is little information regarding the impact of neutralizing M-CSF on GN. In one study, congenital absence of M-CSF in the *op*/*op* mouse did not prevent induction of experimental glomerular injury, although the GN model used appeared to be neutrophil- rather than macrophage-dependent [11]. In addition, the possibility of a beneficial effect of M-CSF expression during renal disease should not be overlooked. M-CSF is required in the neonatal period to establish a normal renal macrophage population, which may be involved in tissue remodeling [12]. Furthermore, some studies have shown that an increase in tissue M-CSF is later followed by an influx of macrophages with immunosuppressive activity [7]. Thus, the expression of M-CSF during renal disease may be important for resolution of inflammation and remodeling of injured tissue. The net effect of M-CSF may depend on when it is expressed in the course of renal disease, the presence of other cytokines, and the genetic background of affected individuals.

While the role of M-CSF in renal inflammation remains to be completely characterized, it is clear from the work of Isbel et al and others that tubular cells can produce immune modulators in vivo, in the absence of GN. An important question is whether attenuation of tubular cytokine production ameliorates renal disease during GN. Recent data address this issue. Tesch et al demonstrated

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Table 1. Immune mediators made by renal tubular cells

Complement components	C3, C4
Chemokines	MCP-1, IL-8, RANTES, IP-10
Cytokines	IL-6, TNF-α, IFN-γ
Growth factors	GM-CSF, M-CSF, PDGF, TGF-β, VEGF

Abbreviations are: MCP-1, monocyte chemoattractant protein-1; IL-8, interleukin-8; RANTES, regulated upon activation, normal T cell expressed and secreted; IP-10, gamma interferon-inducible protein-10; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; IFN-γ, interferon gamma; GM-CSF, granulocyte macrophage colony-stimulating factor; M-CSF, macrophage colony-stimulating factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-beta; VEGF, vascular endothelial growth factor.

that mice genetically deficient in monocyte chemoattractant protein-1 (MCP-1) have significantly less interstitial inflammation and tubular injury during GN than MCP-1–intact mice, but show no improvement in glomerular inflammation [13]. MCP-1 was induced predominantly in the tubules, not the glomeruli of MCP-1–intact mice [13]. In effect, the *MCP-1* gene knockout specifically blocked tubular MCP-1 production in this study. In another investigation, administration of an antisense oligodeoxynucleotide against MCP-1 decreased interstitial inflammation and preserved renal function without altering glomerular pathology in rat anti-GBM GN [14]. The oligodeoxynucleotide was exclusively taken up by proximal tubular epithelial cells, and therefore only inhibited tubular MCP-1 production [14]. Thus, in these experimental models, attenuation of tubular cytokine production is beneficial despite ongoing glomerular injury. These studies also illustrate two important points. First, although glomerular and tubular cells may produce similar pro-inflammatory factors in vitro (e.g., MCP-1), in vivo expression of individual factors may be restricted to a specific compartment. Second, the results of antisense inhibition demonstrate the feasibility of directing therapy to the tubular compartment, and the exciting possibility that blocking inflammation locally can be achieved without systemic immunosuppression.

Taken together, the recent investigations into the role of the renal tubulointerstitium in GN offer compelling evidence that the glomerulus is not necessarily the center of the renal immune universe. Tubules provide an independent contribution to renal inflammation that could determine the ultimate fate of the kidney. Regulation of the tubular cytokine network in vivo remains to be determined. It is not clear whether tubular cells are initially activated directly by the same process that affects glomeruli, or if the pro-inflammatory tubular phenotype is acquired through exposure to proteins, cytokines, or other mediators that filter through, or are made by, injured glomeruli. If tubular epithelium is activated by the glomerulus, it is intriguing to speculate whether the epithelium could become autonomous and maintain production of inflammatory and profibrotic factors after resolution of GN, leading to progressive renal impairment. Understanding these mechanisms should be a high priority in future investigations.

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